Remarks

Claims 1-7 and 19-25 are presently pending in the subject application. By this Amendment, the applicants have amended claim 2 to comply with 37 C.F.R. §1.825. The undersigned avers that no new matter is introduced by this Amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-7 and 19-25 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, a Revocation and New Power of Attorney was previously submitted to the Patent Office by facsimile on October 25, 2002. Enclosed is a copy of the previously submitted Revocation and New Power of Attorney for the Examiner's convenience.

The applicants gratefully acknowledge the Examiner's careful review of the subject specification. By this Amendment, the applicants have renumbered the sequence identifiers, replaced the Brief Description of the Drawings section, and added a Brief Description of the Sequences section in order to facilitate compliance with 37 C.F.R. §1.821-1.825. SEQ ID NOs: 8 and 9 of the previous sequence list (described at page 62 of the specification) were identical to SEQ ID NOs: 4 and 5 (described at page 59) of the specification; therefore, the applicants have renumbered the sequence identifiers to avoid redundancy. The applicants have also added an ATP-binding motif (new SEQ ID NO: 13) to the sequence list, which is described at page 7 of the specification. New SEQ ID NOs: 4-7 are now correctly designated as "artificial sequences" (primers). The descriptions of Figures 42, 43, and 44 now include references to numeric sequence identifiers (new SEQ ID NOs: 10, 11, and 12, respectively).

A Submission of Sequence Listing and Statement under 37 C.F.R. §1.821 accompany this Amendment.

In view of the foregoing remarks and amendments, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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GPL/mv

Attachments: Petition and Fee for Extension of Time
Copy of Communication with accompanying Revocation and New Power of Attorney
Submission of Sequence Listing and Statement Under 37 C.F.R. §1.821
CRF and Paper Copies of Sequence Listing
Copy of Notice to Comply
Marked-up Version of Amended Claim
Marked-up Version of Substitute Paragraphs

Marked-Up Version of Amended Claims

Claim 2(amended):

The construct of claim 1 wherein the metabolite responsive instability element comprises the sequence ~~TAACTCTGAATTTTTAAAACCCGAAGTCAAGAGCTAGTA [SEQ ID NO: 11]~~ of SEQ ID NO: 9.

Docket No.: USF-T135
Serial No.: 09/435,471

Marked-up Version of Substitute Paragraphs

Brief Description Of The Drawings

Figure 1. Schematic representation of the PKC isozymes domain structure

Figure 2. A schematic representation of PKCβ sequence as deduced from the cDNA analysis

Figure 3. Alternative splicing of PKCβ pre-mRNA

Figure 4. PKCβII mRNA is generated via exon inclusion in the alternative splicing of PKCβ

Figure 5. Generation of PKC activators

Figure 6. Activation of PKC by diacylglycerol and Ca+2

Figure 7. Model for activation of PKC

Figure 8. Localization of PKC isozymes by anchoring proteins

Figure 9. Arterial smooth muscle cell phenotypes

Figure 10. Representation of the response-to-injury hypothesis of atherosclerosis proposed by Ross

Figure 11. The MAP kinase pathway transduces the signal from the membrane to the nucleus

Figure 12. The role of phosphoinositide 3-kinase (PI3 kinase) in signal transduction

Figure 13. Levels of eukaryotic gene regulation

Figure 14. The fate of mRNA in mammalian cells

Figure 15. Representation of the structural elements involved in regulating mRNA stability

Figure 16. PKCβI protein levels remain unaltered in the presence of high glucose

Figure 17. PKCβII protein levels decreased by 55% in the presence of glucose

Figure 18. Down regulation of PKCβ(I+II) mRNA by glucose

Figure 19. Map of PKCβ promoter and lengths of deletion constructs

Figure 20. Effect of high glucose on PKCβ deletion constructs

Figure 21. Construct D quenches PKCβ promoter activity at 10h post-synchronization corresponding to S phase

Figure 22. Northern blot analysis of PKCβII mRNA in A10 cells treated with actinomycin D in the presence or absence of high glucose

Figure 23. *In vitro* assay for RNA stability

Figure 24. *In vitro* assay for RNA stability in the presence of EDTA

Figure 25. A schematic representation of the PKCβ as deduced from cDNA sequence analysis

Figure 26. High glucose destabilizes PKCβII mRNA

Figure 27. PKC βII cDNA (350 bp) sequence (SEQ ID NO: 8)

Figure 28. PKC βII cDNA (350 bp) restriction sites map

Figure 29. Effect of glucose and insulin on PKCβII mRNA in aorta smooth muscle cells

Figure 30. Glucosamine does not affect PKCβII mRNA stability

Figure 31. Effect of glucose metabolites on PKCβII MRNA stability

Figure 32. Effect of cycloheximide on glucose-induced PKCβII destabilization

Figure 33. RT-PCR analysis of PKCβI and –βII mRNA after okadaic acid treatment

Figure 34. The pβG-PKCβII chimeric minigene

Figure 35. The pβG-PKCβII chimeric minigene is destabilized by high glucose

Figure 36. Half-life analysis of pβG-PKCβII mRNA

Figure 37. Schematic of the RNA probes used for the RNA EMSAs

Figure 38. RNA electrophoretic mobility shift assay using full length PKCβII mRNA probe

Figure 39. A cytosolic factor binds to a glucose-regulated element present in the PKCβII coding region

Figure 40. No RNA protein binding observed using RNA probe C

Figure 41. UV cross-linking analysis of the RNA-protein binding complex

Figure 42. PKCβII mRNA sequence (SEQ ID NO: 10) and RNA secondary structure analysis

Figure 43. PKCβII mRNA sequence linearized at 175 bp with *Bgl II* (SEQ ID NO: 11) and RNA secondary structure analysis

Figure 44. PKCβII mRNA sequence linearized at 137 bp with *Hpa I* (SEQ ID NO: 12) and RNA secondary structure analysis

Figure 45. Diagram of 3' exons encoding PKCBI and PKCBII via exon inclusion/exclusion and regions of PKCBII exon involved in ~~destablization~~ destabilization of mRNA.

Figure 46. Restriction map of 3' ~~regionof~~ region of PK CBII exon with portions of 3' and 5' flaking exons to be cloned downstream of the cDNA of interest.